Expert Opinion

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Small diameter shunts should lead to safe expansion of the use of TIPS

Jaume Bosch[1,2,3,*]

Summary

Transjugular intrahepatic portosystemic shunt (TIPS) is increasingly used worldwide to treat the complications of portal hypertension in patients with advanced cirrhosis. However, its use is hampered by the risk of causing hepatic encephalopathy and of worsening liver function. The reported haemodynamic targets used to guide TIPS are too narrow to be achieved in most cases and are perhaps not entirely adequate nowadays as they were obtained in the pre-covered stent era. We propose that small diameter TIPS – alone or combined to pharmacological therapy or ancillary interventional radiology procedures – may overcome these limitations while maintaining the beneficial effects of the procedure.

Keywords: Cirrhosis; Portal hypertension; Ascites; Variceal bleeding; Hepatic encephalopathy; Rifaximin; Propranolol; Embolisation of portosystemic collaterals; Splenic artery embolisation.

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Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is almost universally used to treat portal hypertension and its complications when they are not responding to recommended medical therapy, as well as being used in some special situations.[1,2] The most frequent indications for TIPS are currently recurrent variceal bleeding, treatment of acute variceal bleeding in high-risk patients, difficult to treat and refractory ascites, severe portal hypertensive gastropathy, hepatic hydrothorax, portal vein thrombosis and Budd-Chiari syndrome.[3]

From a functional perspective, TIPS is a "calibrated" side-to-side portacaval shunt (like the "H-graft" surgical shunt).[4,5] One potential advantage of TIPS is that it may have less of an effect on liver perfusion because it is constructed in a portal vein branch rather than in the mesenteric vein (as it is in H-graft shunts). As a calibrated shunt, the aim of TIPS is to sufficiently reduce the portacaval pressure gradient (PCG) in order to effectively correct portal hypertension, while (hopefully) maintaining sufficient portal liver perfusion to avoid the development of hepatic encephalopathy and worsening of liver failure.[6] From the early period of surgical shunts, it has been known that a calibrated shunt should be about 8–10 mm in diameter, since larger (12–20 mm diameter) H-graft shunts conferred no advantage over total end-to-side portacaval shunts.[6,7] Moreover, side-to-side and H-graft shunts are known to effectively decompress the liver by allowing retrograde flow through the portal vein, so they are very effective at controlling ascites. This is in contrast with end-to-side portacaval shunts that decompress the liver by decreasing portal perfusion but do not allow retrograde portal flow. These were the premises from which TIPS was developed[8] and soon demonstrated to be effective, feasible, and associated with low peri-operative mortality, to the point that it has almost entirely replaced surgical portal-systemic shunts.[9]

Since its introduction, TIPS technology has improved dramatically, although there is still room to optimise the procedure (Table 1). The most important technical improvement for TIPS was the introduction of polytetrafluoroethylene-covered stents.[10] These have practically abolished the most common drawback of uncovered (metal) stents: TIPS dysfunction due to proliferation of the neo-intima that covers the stent shunt leading to its progressive stenosis/occlusion, which called for close monitoring and re-intervention in over 50% of cases within 6–12 months.[9,11] This form of TIPS dysfunction was much more frequent than TIPS thrombosis, which was common only in patients with pro-coagulant conditions, typically Budd-Chiari syndrome.[12] An important point during deployment of covered stents for TIPS is making sure that the stent is long enough to extend about 2 cm into the portal vein (the uncovered part of the stent), while crossing the intra-parenchymal tract, and the entire length of the hepatic vein until its opening into the inferior vena cava (covered part). Failure to do so may result in TIPS dysfunction owing to the development of stenosis at the non-stented part of the hepatic vein.

Current challenges

Nowadays TIPS dysfunction is no longer a big issue. Current efforts aim at further improving TIPS outcomes, specifically, at decreasing the incidence of

[1]*Department of Biomedical Research, Bern University;*
[2]*Hepatology, University Clinic for Visceral Medicine and Surgery, Inselspital, Bern (CH);*
[3]*University of Barcelona, IDIBAPS and CIBERehd, Barcelona (Spain)*

* Corresponding author. Address: Inselspital, Maurice Müller Haus F 805, Murtenstrasse 35, 3010 Bern, Switzerland.

E-mail address: jaime.bosch@dbmr.unibe.ch (J. Bosch).

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Table 1. Main types of stents for transjugular intrahepatic portosystemic shunt.

Type of stents	Advantages	Disadvantages
Self-expanding uncovered stents	Easy deployment	High incidence of dysfunction
Covered stents (self-expanding)	Not prone to dysfunction	Can continue to expand if under dilated
Controlled-expansion covered stents	Expand only to pre-set diameters (*e.g.* 6-8-10 mm)	

post-TIPS hepatic encephalopathy and liver failure, coming back to the question of how big a TIPS should be to prevent rebleeding/ascites while being small enough not to favour hepatic encephalopathy/liver failure? Unfortunately, the available evidence in this regard is lacking and mostly comes from observations in the era of uncovered stents.[11]

Factors influencing the fall in portal pressure gradient after TIPS (Fig. 1)

Increasing stent diameter is the easiest way of decreasing PCG when placing a TIPS. This is because according to *Poiseuille's Law*, the most important factor determining resistance (R) to flow in a blood vessel is its radius (r)

$$quadquadquadquadquadquadquadquadR = 8\ L \times \eta / r^4$$

The other variables in the equation are blood viscosity (η) (relatively stable in normal circumstances), and vessel length (L). Length is much less important than diameter, since it increases resistance in an arithmetic way, while resistance (and therefore PCG) is inversely related to the radius at the fourth power. This explains why "bended" C-shaped TIPS (usually to a branch of the right portal vein) are less effective than "straight" TIPS, since at the bending zone the cross-sectional shape of the stent-TIPS is not circumferential but elliptical (smaller compared to a circular shunt), leading to a much higher resistance and PCG. Therefore, straight, "central" TIPS between the main right hepatic vein and the right portal vein are more effective at decreasing the PCG than peripheral shunts (Fig. 1).

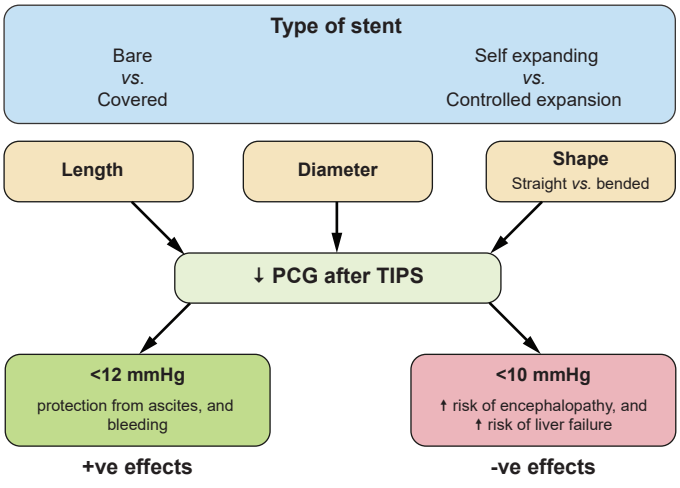

Fig. 1. Factors influencing the effects of TIPS on the PCG. Considerations for the clinical application of TIPS. PCG, portocaval pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

How much shall we decrease the PCG to prevent/correct complications of portal hypertension?

Do we still need to decrease PCG to <12 mmHg or by more than 50%?

Studies have shown that PCG should be decreased to 12 mmHg or below,[11] or by over 50% of baseline (which in most cases means a PCG <12 mmHg)[9] to prevent the complications of portal hypertension. This comes from careful observations showing that recurrent bleeding and ascites occurred almost exclusively when patients had a PCG of at least 12 mmHg after TIPS. Accordingly, it was recommended to dilate the stent shunt until PCG was ≤12 mmHg. This seems simple, but it is not, since first, PCG should be measured correctly, between the portal vein and the inferior vena cava (not between the portal vein and the right atrium, as most interventional radiologists used to do).[13] Since the right atrial pressure is always lower than the inferior vena cava pressure, the porta-atrial gradient overestimates the PCG, which may lead to excessive stent dilatation. Second, sedation and/or anaesthesia for TIPS frequently precludes correct measurements of the PCG,[14] which requires post-TIPS measurements after the effects of anaesthesia are gone or the day after,[15] increasing the burden and cost of TIPS, as well as requiring interventional radiologists to recognise that accurate haemodynamic measurements rather than radiological images should guide their decisions. Moreover, when using general anaesthesia, much care should be given to avoid hypotension, which prevents accurate measurements of portal pressure gradient[14] and may potentiate the reduction in liver perfusion and contribute to post-TIPS liver failure.

How small should TIPS diameter be to avoid hepatic encephalopathy?

What is a beneficial fall in PCG after TIPS using current improved stents?

A large proportion of patients developing severe encephalopathy after TIPS have quite low PCG (5–10 mmHg), suggesting a very narrow therapeutic window: below 12 mmHg to be effective, above 10 mmHg to decrease the likelihood of encephalopathy.[11] In practice, this target may be difficult to reach. Indeed, clinical practice is to dilate the TIPS until achieving an effective reduction in portal pressure. In case of a gradual dilatation, if – for instance – the PCG drops to 13 mmHg after dilating the stent to 8 mm, it is likely that after dilating to 10 mm the final PCG might be too

low (say 6–7 mmHg). In this case the patient should be carefully observed for encephalopathy and post-TIPS worsening of liver failure, receive early treatment with lactulose and rifaximin, and if severe encephalopathy/deterioration of liver function occurs, a "TIPS reduction" should be planned. This procedure requires co-axial re-stenting with a covered stent of smaller diameter[16] (and sometimes placement of a parallel ["tandem"], shorter, external stent that is dilated to compress the TIPS until the PCG reaches "safe" values).

It is important to note that most studies on haemodynamic targets were done before the introduction of covered stents and have not been adequately updated since then. Why does this matter? Uncovered stents, as mentioned above, predictably tend to decrease in diameter over time, so the decrease in PCG achieved after TIPS is not sustained, but progressively lost over time until re-intervention (TIPS angioplasty or re-stenting).[11] In contrast, with TIPS using covered stents, the pressure drop is maintained during follow-up.[10] It is conceivable therefore that when using uncovered stents, a greater (possibly excessive) PCG reduction was required to maintain the PCG ≤12 mmHg over time. In other words, it is likely that covered stents of lower diameter (causing a smaller fall in PCG) could be as effective as larger uncovered stents. This might in part explain the discrepancy between a "good haemodynamic response" to pharmacological therapy (a decrease in hepatic venous pressure gradient of at least 20% from baseline or below 12 mmHg)[17] and a good response to TIPS (a 50% decrease in PCG or to values ≤12 mmHg).[11] At this point, it is worth remembering that what is a good haemodynamic response to covered TIPS has not been adequately studied, since most studies used the same PCG targets as for uncovered TIPS.

To further complicate these issues, several studies indicate that self-expandable stents may continue to dilate until achieving their nominal diameter.[18,19] This means that if the PCG is 11 mmHg after dilating a 10 mm stent to only 8 mm, the stent may continue to self-dilate until reaching approximately 10 mm in diameter, leading to a further decrease in PCG and an increased risk of encephalopathy. How frequently this spontaneous expansion is clinically relevant is a matter of debate, but certainly represents a limitation. This led to a further technical improvement, the "controlled-expansion" stents, that cannot spontaneously dilate over pre-set limits (controlled by an external sheath).[16,20]

The bottom line is that with these technical improvements, it is now feasible to perform a calibrated shunt that will maintain its diameter over time. However, we are still very far from perfection, since we do not have an answer for simple questions such as how large the shunt should be, or what PCG reduction should be targeted to prevent recurrent bleeding or ascites? Certainly, the target PCG reduction should probably be less than that required in the uncovered stent era, but specific data to guide evidence-based decisions are lacking.

Regarding the risk of developing hepatic encephalopathy and post-TIPS worsening of liver failure we are also in uncertain territory. From the experience with H-graft calibrated shunts we know that 8 mm shunts were significantly better than large shunts (12 mm and above).[6,21] For TIPS, it has recently been reported that under-dilated covered TIPS (dilated to up to 6–7 mm in diameter) may cause less encephalopathy than "standard" diameter TIPS (8–10 mm in diameter),[22] but this is based on a single non-randomised retrospective study with a rate of overt hepatic encephalopathy of 54% at 1-year with standard TIPS (in the upper reported range) and of 26.9% with under-dilated TIPS. Moreover, the study reported no spontaneous dilation of the self-expandable stents, which contrasts with the results of studies conducted over longer observation times.[18] Better results could probably be achieved with controlled-expansion stents. Based on the limited data available, the best "small diameter" TIPS to prevent or minimise the incidence of encephalopathy, while effectively preventing rebleeding and/or ascites, should be about 6–8 mm, but a "one-size-fits-all" strategy is most likely unrealistic.[21,23] Similarly, it is unknown whether other parameters linked to outcomes in cirrhosis, such as age, quantitative liver function tests, liver/spleen stiffness or volume, heart function, inflammation, bacterial translocation and malnutrition/sarcopenia, may be factored into a decision-making algorithm that balances between keeping the shunt as small as possible while sufficiently reducing PCG. An additional advantage of using small diameter TIPS is that it may decrease the incidence of post-TIPS heart failure.[24] Small diameter TIPS would likely also diminish the risk of aggravating liver failure after TIPS. In most cases this is mild and transient, gradually fading within 3 weeks of the TIPS procedure, and is most likely related to a reduction of effective liver perfusion with portal blood, which can be aggravated by hypotension during the procedure. Radiation hepatitis may be a potential concern in difficult/long procedures.

What else can we do to prevent post-TIPS encephalopathy? Expert recommendations

Is there any further improvement that we could introduce? Challenging aspects are summarised in Box 1. Reported haemodynamic targets are currently too narrow to be achieved in most cases, and perhaps not entirely adequate nowadays, as they were mostly obtained in the pre-covered stent era. I hypothesise that what required a PCG reduction to below 12 mmHg or >50% of baseline using uncovered stents could be achieved with a PCG decrease to say 14 mmHg or >30% of baseline.

Box 1. Challenging aspects in TIPS.

Pending questions:

- Do we still need to decrease PCG <12 mmHg or by more than 50%?
- What defines a beneficial fall in PCG after TIPS using current improved stents?
  - *we rely on old data!*

Answers:

a. Less can be more: use small diameter TIPS (6-8 mm diameter) even if final PCG slightly above 12 mmHg
   - *less HE doesn't need to be matched by more bleeding/ascites*
   - *may decrease the incidence of heart failure after TIPS*

b. Optimize the benefit of the decrease in PCG
   - *by associating drugs*
   - *by associating procedures*
   - *by life-style intervention and other*

HE, hepatic encephalopathy; PCG, portacaval pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

This goal is obtained in a large proportion of patients with small diameter TIPS that are likely to result in less worsening of portal-systemic shunting and hence a lower likelihood of severe encephalopathy and post-TIPS liver failure.[20,21,23] Of note, in high-risk situations, such as refractory ascites, the recent EASL guidelines already recommended small diameter TIPS, although not suggesting TIPS as small as 6 mm.[25]

According to this hypothesis, studies should assess the effectiveness of small diameter TIPS (of 6 mm [or 7 mm] in diameter) complemented by either drug therapy, an associated procedure, or both, with the aim of reducing PCG by 30% of baseline or to ≤14 mmHg. The goal would be to avoid an additional stent dilation (to 8–10 mm) that may cause the portal pressure gradient to decrease too much, hence increasing the risk of encephalopathy, liver failure and/or heart failure. This would require availability of controlled-expansion covered stents of 6 mm initial diameter (expandable to 8 mm), reserving 8 mm stents (expandable to 10 mm) for patients with poor TIPS alignment.

Complementing a small diameter TIPS with drugs

We first studied this some years ago and found that an "insufficient" fall in PCG after TIPS (which may occur even with fully expanded stents) can be converted into a "satisfactory" one by adding propranolol, even at relatively low doses.[26] Why? Very schematically, because of the synergistic effect of combining two different mechanisms to decrease PCG: TIPS decreases the PCG by bypassing liver resistance to portal flow, while propranolol decreases PCG by reducing splanchnic blood flow. In addition to our published experience, we (among others) have successfully used this approach clinically with good results.[26]

Complementing a small diameter TIPS with associated procedures

I am referring here primarily to something that is common practice in many centres and consists of embolising collaterals that remain wide open after TIPS. After using a small diameter TIPS to reach a final PCG of about 14 mmHg, occlusion/embolisation of large collaterals feeding the varices has the potential to not only increase efficacy (for instance, occlusion of the left gastric vein dramatically decreases blood flow to oesophageal varices), but also to decrease the likelihood of severe encephalopathy.[27] This can be particularly valuable in patients that cannot tolerate or are poor candidates for non-selective beta-blockers due to hypotension, the presence of relative contra-indications or associated conditions.

Optimising the candidate for TIPS

It is worth noting that post-TIPS encephalopathy is a complex condition that is not only determined by TIPS diameter but by a myriad of non-haemodynamic factors. Age, degree of liver and kidney failure, chronic inflammation, urease-producing intestinal bacteria, bacterial translocation and malnutrition/sarcopenia, are other very important factors that can modulate the therapeutic effort.[3] Several of them are associated not only with post-TIPS encephalopathy, but also with post-TIPS survival.[3] Administration of rifaximin, started before TIPS, was shown to be effective in a recent randomised controlled trial,[28] leading to a 40% reduction in cases of hepatic encephalopathy. Pre-habilitation (*e.g.* improving malnutrition before TIPS) and rehabilitation (*e.g.* adding supervised moderate exercise to nutrition after TIPS) could be extremely important. Finally, a strict follow-up of patients undergoing TIPS for refractory ascites enables the need for diuretics to be tailored to avoid dehydration, a relatively frequent cause of encephalopathy 1–3 weeks after TIPS. Carefully explaining avoidable triggers and warning signs (*e.g.* dehydration, constipation, hypoglycaemia in diabetics, early identification of bacterial infection, including periodontitis) to patients and their relatives is mandatory before discharge.[3] A combination of all these strategies should be attempted to further improve outcomes in this particular population.

What I would not recommend

The procedure that I do not recommend is splenic artery embolisation, since its effects may be transient (if this is a proximal embolisation) and the procedure may cause severe complications.[29] A similar or greater decrease in portal blood flow can be much more safely achieved by administering propranolol.

Abbreviations

PCG, portacaval pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflicts of interest

The author is a consultant for Actelion, Ambys, BioVie, BLB, BMS, Brudy, Chiasma, Exalenz and Surrozen, and has received speaking fees from Gore.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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